Response of Cultured Vascular Endothelial Cells to Fluid Flow

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In our previous experiment using the canine common carotid artery shunted with the external jugular vein, it has been clarified that arterial wall alters its internal diameter against sustained blood flow changes, so as to maintain the wall shear stress constant. This response has been confirmed to be initiated from the endothelial cell layer directly contacting blood flow. Our recent in vitro studies using cultured endothelial cells have shown that their proliferative and migrative activities are facilitated by fluid shear stress elicited to the cell layer with the culture medium flow. Similar effects of fluid shear stress on the synthetic and secretory activities of the endothelial cells have been reported. However, it has not been clearly defined how endothelial cells sense mechanical forces acting on the cell membrane and modulate their functions. To clarify this point, we applied fluid flow to cultured endothelial cells in a specially designed flow chamber and examined changes in cytoplasmic free Ca^{++} level ($[Ca^{++}]_i$), a major component of the intracellular information transmission system of the cell. We also examined changes in $[Ca^{++}]_i$ when frictional force, a physical stimulus other than flow, was applied to endothelial cell membranes by rubbing them with a balloon. Application of flow (shear stress 0.1-20 dyn/cm^2) to cells by medium perfusion led to an immediate several times increase in $[Ca^{++}]_i$, and when flow stopped, $[Ca^{++}]_i$ returned to the resting level. Extracellular ATP in the perfusate was involved in this flow-induced Ca^{++} response, and a flow-rate or shear-stress dependency of Ca^{++} response was seen at around 500 nM ATP. Although Ca^{++} transients occurred when endothelial cell membrane was rubbed lightly with a balloon (shear stress > 200 dyn/cm^2), extracellular ATP did not participate in the friction-induced Ca^{++} response. These results suggest the presence of an endothelial cell mechanism by which changes in flow or mechanical shearing force acting on the cell membrane are recognized as a stimulus, and the information is converted into changes in $[Ca^{++}]_i$.